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EXAMINER	
SCHMIDT, MARY M	

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1635	31

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Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No. 08/978,637	Applicant(s) RABBANI ET AL.	
	Examiner Mary M. Schmidt	Art Unit 1635	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *06 January 2003* .

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *245-280,282-284 and 286-317* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *245-280,282-284 and 286-317* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *25 November 1997* is/are: a)☐ accepted or b)☒ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449) Paper No(s) *30* .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: .

DETAILED ACTION

1. The restriction requirement mailed 12/3/02 is withdrawn. Claims 245-280, 282-284 and 286-317 are pending.

Drawings

2. The drawings dated 11-25-97 were reviewed by an Official draftsman and the PTO-948 with required corrections was attached to the Office action, 12/03/02. Applicant needs to provide corrected drawings.

Claim Objections

3. Claims 247, 278, 301 and 302, line 3 in each, is objected to since they twice claim "a phage, a phage..." in a row.

4. Claim 307 is objected to for the language "or or" in line 3.

5. Claim 246 does not further limit claim 245 since claim 245 is drawn to a composition comprising a primary nucleic acid component for introduction into a eukaryotic cell, and claim 246 states that the cell is eukaryotic. Furthermore, claim 246 lacks antecedent basis for the recitation of the limitation wherein the cell is prokaryotic, since the parent claim 245 states that the cell is eukaryotic, and the cell must be one or the other, it can not be a member of both kingdoms (Monera for prokaryotes and Animalia for eukaryotes).

Also, in claim 246, "eukaroytic" is misspelled and should read "eukaryotic".

Claim Rejections - 35 USC § 112

6. Claims 245-280, 282-284 and 286-317 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

Claim 245 is drawn to a composition comprising a primary nucleic acid component which upon introduction into a eukaryotic cell produces a secondary nucleic acid component which is capable of producing a nucleic acid product, or a tertiary nucleic acid component, or both, in said eukaryotic cell, wherein said primary nucleic acid component is not obtained with said secondary or tertiary component or said nucleic acid product. Claim 246 specifies that the cell is eukaryotic or prokaryotic. Claim 247 specifies that the primary nucleic acid component is selected from a nucleic acid, a nucleic acid construct, a nucleic acid conjugate, a virus, a viral fragment, a viral vector, a viroid, a phage, a plasmid, a plasmid vector, and a bacterial fragment, or a combination of the foregoing. Claim 248 states that the primary nucleic acid component is single-stranded, double-stranded or partially double-stranded. Claim 249 states that the primary nucleic acid component is selected from the group consisting of DNA, RNA, nucleic acid analogs, and a combination thereof. Claim 250 states that wherein said DNA, RNA or both are modified. Claim 251 states that the secondary nucleic acid component or said tertiary nucleic

acid component is selected from the group consisting of DNA, RNA, a DNA-RNA hybrid, a DNA-RNA chimera, and a combination of the foregoing. Claim 252 states that the composition of claim 245 further comprises a signal processing sequence. Claim 253 states that the signal processing sequence is selected from the group consisting of a promoter, an initiator, a terminator, an intron, a cellular localization element, and a combination of the foregoing. Claim 254 states that the signal processing element is contained in an element selected from the group consisting of said primary nucleic acid component, said secondary nucleic acid component, said nucleic acid product, said tertiary nucleic acid component and a combination of the foregoing. Claim 255 states wherein said nucleic acid product is single-stranded. Claim 256 states wherein said nucleic acid product is selected from the group consisting of antisense RNA, antisense DNA, a ribozyme, a protein binding nucleic acid sequence, and a combination of the foregoing. Claim 257 states that the protein binding nucleic acid sequence comprises a decoy that binds a protein required for viral assembly or viral replication. Claim 258 states that the component or nucleic acid production is mediated by a vector. Claim 259 states that the vector is selected from the group consisting of a viral vector, a phage vector, a plasmid vector, and a combination thereof.

Claim 260 is drawn to a cell containing the composition of claim 245. Claim 261 states that the cell is eukaryotic. Claim 262 states that the cell has been introduced *ex vivo* into said cell. Claim 263 states that the composition has been introduced *in vivo* into said cell.

Claim 264 is drawn to a secondary or tertiary nucleic acid component or nucleic acid product produced from the composition of claim 245.

Claim 265 is drawn to a composition of matter comprising a nucleic acid component which when present in a cell produces a non-natural nucleic acid product, which product comprises (I) a cellular compartment localizing entity, and (ii) a nucleic acid sequence of interest. Claim 266 states that the cellular compartment localizing entity (I) is sufficient to permit localization of said non-natural nucleic acid product. Claim 267 states the localizing entity (I) comprises a nuclear localization signalling sequence. Claim 268 states that the nucleic acid of interest (ii) is selected from the group consisting of DNA, RNA, a DNA-RNA hybrid, a DNA-RNA chimera, and combination of the foregoing. Claim 269 states that RNA comprises a nuclear localized RNA complexed with protein molecules. Claim 270 states that the nuclear localized RNA comprises a snRNA. Claim 271 states that the snRNA comprises U1 or U2, or both. Claim 272 states that the non-natural nucleic acid product is single-stranded. Claim 273 states that the non-natural nucleic acid product is selected from the group consisting of antisense RNA, antisense DNA, sense RNA, sense DNA, a ribozyme, a protein binding nucleic acid sequence, and a combination of the foregoing. Claim 274 states that protein binding nucleic acid sequence comprises a decoy that binds a protein required for a viral assembly or viral replication. Claim 275 states that the non-natural nucleic acid product comprises antisense RNA or antisense DNA and the localizing entity (I) comprises a nuclear localization signalling sequence. Claim 276 states the non-natural nucleic acid product comprises antisense RNA or antisense DNA and

the localizing entity (I) comprises a cytoplasmic localization signalling sequence. Claim 278 states the nucleic acid component of claim 265 is selected from a nucleic acid, a nucleic acid construct, a nucleic acid conjugate, a virus, a viral fragment, a viral vector, a viroid, a phage, a phage, a plasmid, a plasmid vector, and a bacterial fragment, or a combination of the foregoing. Claim 279 states wherein said nucleic acid is selected from the group consisting of DNA, RNA, a DNA-RNA hybrid, a DNA-RNA chimera, and a combination of the foregoing. Claim 280 states the composition of claim 278, wherein the nucleic acid is modified. Claim 282 states the composition of claim 265, wherein the production of said nucleic acid product is mediated by a vector. Claim 283 states the composition of claim 282, wherein the vector is selected from the group consisting of a viral vector, a phage vector, a plasmid vector and a combination thereof.

Claim 284 is drawn to a cell containing the composition of claim 265. Claim 286 states the claim cell of claim 284, wherein said composition has been introduced *ex vivo* into said cell. Claim 287 states the cell of claim 284 wherein the composition has been introduced *in vivo* into said cell. Claim 288 is drawn to a biological system containing the cell of claim 284. Claim 289 states that the system is selected from the group consisting of an organism, an organ, a tissue, a culture, and a combination thereof.

Claim 290 is drawn to a process for localizing a nucleic acid product in a eukaryotic cell, comprising:

(A) providing a composition of matter comprising a nucleic acid component which when present in a cell produces a non-natural nucleic acid product, which product comprises:

(I) a portion of a localizing entity, and

(II) a nucleic acid sequence of interest; and

(B) introducing said composition into said cell or into a biological system containing said cell.

Claim 291 states the process of claim 290, wherein said potion of the localizing entity (I) is sufficient to permit localization of said nucleic acid product. Claim 292 states the process of claim 290, wherein said nucleic acid product comprises antisense RNA or antisense DNA and said portion of a localizing entity (I) comprises a nuclear localization signalling sequence. Claim 293 states the process of claim 290, wherein said nucleic acid product comprises sense RNA or sense DNA and said portion of a localizing entity (I) comprises a nuclear localization signalling sequence. Claim 294 states wherein said nucleic acid product comprises sense RNA or sense DNA and said portion of a localizing entity (I) comprises a nuclear localization signalling sequence. Claim 295 states the process of claim 290, wherein said nucleic acid product comprises snRNA. Claim 296 states the process of claim 295, wherein said snRNA comprises U1 or U2 or both. Claim 297 states the process of claim 290, wherein said composition is introduced *ex vivo* into said cell or into a biological system containing said cell. Claim 298 states the process of claim 290, wherein said composition is introduced *in vivo* into said cell or into a biological system containing said cell.

Claim 299 is drawn to a nucleic acid component which upon introduction into a cell is capable of producing more than one specific nucleic acid sequence, each such specific sequence

so produced being substantially nonhomologous with each other and being either complementary with a specific portion of a single-stranded nucleic acid of interest in a cell or capable of binding to a specific protein of interest in a cell. Claim 300 states the component of claim 299, wherein said single-stransded nucleic acids of interest are part of the same polynucleotide sequence or part of different polynucleotide sequences. Claim 301 states that the nucleic acid component of claim 299, wherein said single-stranded nucleic acid of interest comprise a viral sequence. Claim 302 states the nucleic acid component of claim 299, wherein said component is derived or selected from a nucleic acid, a nucleic acid construct, a nucleic acid conjugate, a virus, a viral fragment, a viral vector, a viroid, a phage, a phage, a plasmid, a plasmid vector, and a bacterial fragment, or a combination of the foregoing. Claim 303 states the composition of claim 299, wherein the nucleic acid is selected from the group consisting of DNA, RNA, nucleic acid analogs, and a combination thereof. Claim 304 states the nucleic acid of claim 303, wherein said DNA or RNA is modified. Claim 305 states the nucleic acid component of claim 299, comprising either more than one promoter or more than one initiator, or both. Claim 306 states the nucleic acid component of claim 299, wherein each said specific nucleic acid sequence product is capable of being produced independently from either different promoters, different initiators, or a combination of both. Claim 307 states the nucleic acid component of claim 299, wherein said specific nucleic acid sequence products are either complementary to a viral or cellular RNA, or bind to a viral or cellular protein, or a combination of the foregoing. Claim 308 states the nucleic acid component of claim 307, wherein said complementary specific nucleic

acid sequence products are capable of acting as antisense. Claim 309 states the nucleic acid component of claim 308, wherein said viral or cellular protein comprises a localizing protein or a decoy protein. Claim 310 states the nucleic acid component of claim 309, wherein said localizing protein comprises a nuclear localizing protein or a cytoplasmic localizing protein. Claim 311 states the nucleic acid component of claim 309, wherein the decoy protein binds a protein required for viral assembly or viral replication. Claim 312 states the composition of claim 299, wherein said specific nucleic acid products are selected from the group consisting of antisense RNA, antisense DNA, a ribozyme, a protein binding nucleic acid sequence, and a combination of the foregoing. Claim 313 states the nucleic acid component of claim 299, further comprising a means for delivering said component to a cell containing the nucleic acid of interest or the specific protein of interest.

Claim 314 is drawn to a construct which when present in a cell produces a product, said construct being bound non-ionically to an entity comprising a chemical modification or a ligand. Claim 315 states the construct of claim 314, having at least one terminus, said terminus comprising a polynucleotide tail. Claim 316 states the construct of claim 315, wherein said polynucleotide tail is hybridized to a complementary polynucleotide sequence. Claim 317 states the composition of claim 245, wherein said secondary nucleic acid is DNA and said tertiary nucleic acid is RNA.

The specification teaches several constructs designed for entry into a cell and expression of one or more sequences to perform a biological function such as antisense inhibition of a

nucleic acid. Specifically, several CHENAC constructs are taught prophetically, and pictured in figures 1-13 as vector based constructs constructed by using modified nucleic acid regions and designed to provide improved entry into a cell by way of improved construct-cell interaction. A second group of nucleic acid fused with antibody based constructs are taught prophetically and shown in figures 14-21. Preparation of multimeric insulin by means of nucleic acid hybridization is further taught prophetically and shown in figures 22-23. No exemplification for such constructs is taught in the specification as filed.

Furthermore, vectors ultimately designed for antisense inhibition of HIV in cells by co-expression of antisense DNA under control of a T7 promoter with a T7 polymerase (represented in figures 24-49) are taught and supported by *in vitro* data. Specifically, construction of the M13 phage vectors pRT-A, pRT-B, and pRT-c are taught which contain the coding sequence for the T7 RNA polymerase driven by the RSV promoter and with an SV40 intron sequence that will be spliced out to form a functional polymerase enzyme and each respective construct also having the antisense A, B, and C sequences driven by a T7 promoter and terminated by a T7 terminator. A modified version of the pINT-3 construct (the parent vector of pRT-A, B and C vectors before insertion of the antisense sequences) is taught where a polylinker is inserted behind the poly-A tail of the T7 polymerase gene for subsequent sub-cloning of the lacZ gene in this instance to form pINT-LacZ. The result upon introduction in a eukaryotic cell would be synthesis of the T7 polymerase from the RSV promoter which in turn acts upon the T7 promoter to synthesize B-galactosidase.

Furthermore, plasmids are taught containing anti-sense segments introduced into the transcript region of the U1 gene, plasmid pHSD-4 U1 so that upon expression of the transcript, the antisense RNA sequence is produced to the complementary region of the HIV genome. Specifically, pDU1-A, B, C and D were made using the antisense A, B, and C sequences previously described and D as a control containing a non-HIV sequence. A multi-cassette version of the constructs was also made by sub-cloning in tandem the A,B, and C antisense to make pNDU1 (A,B,C) (N meaning the construct was also contained the gene for neomycin resistance).

Other multi-cassette constructs taught were:

(1) TRI 101, an M13 phage vector containing the "A" antisense T7 operon , the "B" antisense T7 operon and the "C" antisense T7 operon in a single construct (figure 46). Co-transfection would be required for expression of the antisense molecules from this construct with a vector that expresses T7 RNA polymerase (suggested is the intron containing construct of example 19); and,

(2) an M13 construct constructed from a multi-ligation of portions of pINT-3 (containing the intron containing polymerase) and the T7 promoter driven A, B, and C sequences (see figure 47).

The specification teaches application of some of these constructs ("various U1 constructs described above" p. 167, last line) in antisense inhibition of HIV in infected U937 cell culture. Specifically the following is shown: (1) expression of A, B, and C antisense by hybridization analysis after expression of the "U1 clone" (p. 169, line 3), (2) expression of the "triple U1

construct" (p. 169, para. (c), line 1) which result in a decrease in p24 production next to the control, and increased % reduction in p24 over time and after re-infection of cells, and these results were confirmed by absence p24 amplification next to control cells via PCR of the targeted DNA, and (3) expression of the construct of figure 50, a fusion product antisense A upstream of B-gal gene where antisense activity of the A portion caused inhibition of B-gal activity as shown in lacZ assays. The results in figure 51 show HIV A/Anti-A activity and HIV A/Anti-ABC (when the triple U1 construct was used by *co-transfection*) as the equivalent of the uninfected cells whereas the infected and control containing cells showed high B-gal expression. Therefore, it does not appear in the specification as filed that the multicassette A,B,C and T7 polymerase construct (expressed on same plasmid) was applied to the same HIV challenge experiments.

Additional constructs are more prophetically taught: the primary nucleic acid construct that propagates production centers for the production of single-stranded antisense, etc. in examples 21-25, and the retrovirus vector containing sequences for the expression of antisense RNA directed at HIV on page 181, last para.

MPEP 2163 teaches the following conditions for the analysis of the claimed invention at the time the invention was made in view of the teachings of the specification and level of skill in the art at the time the invention was made:

> The claimed invention as a whole may not be adequately described where an invention is described solely in terms of a method of its making coupled with its function and there is no described or art-recognized correlation or relationship between the structure of the invention and its function. A biomolecule sequence described only by a functional characteristic, without any known or disclosed correlation between that function and the

> structure of the sequence, normally is not a sufficient identifying characteristic for written description purposes, even when accompanied by a method of obtaining the claimed sequence....A lack of written description issue also arises if the knowledge and level of skill in the art would not permit one skilled in the art to immediately envisage the product claimed from the disclosed process....Generally, there is an inverse correlation between the level of skill and knowledge in the art and the specificity of disclosure necessary to satisfy the written description requirement....The written description requirement for a claimed genus may be satisfied through sufficient description of a representative number of species by actual reduction to practice..., reduction to drawings..., or by disclosure of relevant, identifying characteristics, i.e., structure or other physical and/or chemical properties, by functional characteristics coupled with a known or disclosed correlation between function and structure, or by a combination of such identifying characteristics, sufficient to show the applicant was in possession of the claimed genus.

The claims lack written description since a representative number of species of the constructs claimed for use in a cell are not adequately described by the specification as filed. The claims are drawn to the following independently claimed compositions: (1) claim 245: compositions comprising a nucleic acid component which upon introduction into a eukaryotic cell produces a secondary nucleic acid component which is capable of producing a nucleic acid product, or a tertiary nucleic acid component, or both, in said eukaryotic cell, wherein said primary nucleic acid component is not obtained with said secondary or tertiary component or said nucleic acid product; (2) claim 265: a composition of matter comprising a nucleic acid component which when present in a cell produces a non-natural nucleic acid product, which product comprises (I) a cellular compartment localizing entity, and (ii) a nucleic acid sequence of interest; (3) claim 299: a nucleic acid component which upon introduction into a cell is capable of producing more than one specific nucleic acid sequence, each such specific sequence so

produced being substantially nonhomologous with each other and being either complementary with a specific portion of a single-stranded nucleic acid of interest in a cell or capable of binding to a specific protein of interest in a cell; (4) claim 314: a construct which when present in a cell produces a product, said construct being bound non-ionically to an entity comprising a chemical modification or a ligand. As summarized above, one of skill in the art must be able to "immediately envisage the product claimed from the disclosed process..." Although, the specification as filed has shown (in the figures especially), numerous vector-like constructs, the only species shown to produce a product in a cell is that of the intron containing vector constructs for expression of an antisense to HIV expressed therefrom in a cell in cell culture. One of skill in the art would not have recognized that applicant was in possession of a representative number of other species of the broad genus of constructs claimed having other nucleic acid elements which are produced upon expression in a cell. In regards to the breath of antisense claimed, design of an antisense is based on knowledge of the target gene nucleic acid structure. One of ordinary skill in the art would not have recognized that applicant was in possession of a representative number of species of antisense (or ribozyme) to any target gene from the teachings of the specification as filed. Thus, absent further specific (not general) guidance for the nucleic acid structure of other vector constructs which produce a product in a cell. Furthermore, neither the specification nor the prior art taught a representative number of species of the claimed constructs having the function of use in cells in a whole organism, via administration either *in vivo* or *ex vivo*. The examples in the instant specification as filed do not

teach the direct correlation between any such vector constructs (including the U1-anti-HIV constructs) as having a specific function in a cell in a whole organism.

Response to Arguments

7. Applicant's arguments filed June 19, 2002, have been fully considered but they are not persuasive.

Applicants "assert that adequate description has been provided. A detailed description of the constructs for producing products in accordance with the present invention is described in the present specification and includes working examples and figures.... Sufficient identifying characteristics of the constructs, compositions and kits of the present invention is provided as noted above in the specification. Additionally, a sufficient number of species have been disclosed. Moreover, the terminology employed by Applicants to describe their constructs (page 169) is accepted in the art, and as such, should be deemed to satisfy the written description test under the law."

In response, although actual reduction to practice is not required to adequately describe the claimed invention, one of skill in the art must be able to readily envisage both the breath of the genus of claimed constructs as well as the representative number of species of any such genus of constructs as defined by certain common attributes and features. In the instant case, the constructs are nucleic acid constructs which when present in a cell produce a product as well as other possible products. This genus claimed embraces the production of a product in any cell.

Not all cells are alike, and the environmental conditions alter drastically from use of cells in cell culture to use of cells in a whole organism which are intimately connected to other cells in the whole organism. Thus, the genus of cells in which the nucleic acid constructs are expressed is critical to understanding the genus of the claimed constructs since the claims have the function limitation that the nucleic acid construct is introduced into a cell and codes for and expresses a non-native nucleic acid. Additionally, to understand the breath of the claimed genus, one of skill in the art must consider the breath of the nucleic acid constructs claimed. Typically in the art, only a vector-type construct is capable of having the function of coding for and expressing a nucleic acid product from the encoding nucleic acid gene sequence. Since nucleic acid constructs are composed of nucleic acids, having a defined sequence of bases, one of skill in the art would not readily envisage any such nucleic acid construct absent the nucleic acid sequence of said construct. Thus, the claimed genus is extremely broad since it is drawn to any possible nucleic acid construct expressing in a cell. And since the specification as filed does not further provide the essential material of defining the common elements of nucleic acid sequence structure of any such nucleic acid composition, one of skill in the art does not have a clear vision of a representative number of species of any such nucleic acid construct. The invention should be clearly defined in the specification as filed and essential material to the claimed invention (such as the nucleic acid sequences of the claimed nucleic acid constructs) can only be incorporated by reference to a patent publication (see MPEP 608.01(p)(A)). Thus, the claims are not adequately described by the specification as filed for the breath of claimed constructs.

8. Claims 260-263 and 284-298 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for methods of selectively expressing a nucleic acid product in a cell in cell culture (*in vitro*), does not reasonably provide enablement for methods of expressing the nucleic acids in a whole organism (*in vivo*). The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention commensurate in scope with these claims.

Claim 260 is drawn to a cell containing the composition of claim 245. Claim 261 states that the cell is eukaryotic. Claim 262 states that the cell has been introduced *ex vivo* into said cell. Claim 263 states that the composition has been introduced *in vivo* into said cell. (Claim 245 is drawn to a composition comprising a primary nucleic acid component which upon introduction into a eukaryotic cell produces a secondary nucleic acid component which is capable of producing a nucleic acid product, or a tertiary nucleic acid component, or both, in said eukaryotic cell, wherein said primary nucleic acid component is not obtained with said secondary or tertiary component or said nucleic acid product.)

Claim 264 is drawn to a secondary or tertiary nucleic acid component or nucleic acid product produced from the composition of claim 245.

Claim 284 is drawn to a cell containing the composition of claim 265. Claim 286 states the claim cell of claim 284, wherein said composition has been introduced *ex vivo* into said cell. Claim 287 states the cell of claim 284 wherein the composition has been introduced *in vivo* into

said cell. Claim 288 is drawn to a biological system containing the cell of claim 284. Claim 289 states that the system is selected from the group consisting of an organism, an organ, a tissue, a culture, and a combination thereof. (Claim 265 is drawn to a composition of matter comprising a nucleic acid component which when present in a cell produces a non-natural nucleic acid product, which product comprises (I) a cellular compartment localizing entity, and (ii) a nucleic acid sequence of interest.)

Claim 290 is drawn to a process for localizing a nucleic acid product in a eukaryotic cell, comprising:

(A) providing a composition of matter comprising a nucleic acid component which when present in a cell produces a non-natural nucleic acid product, which product comprises:

(I) a portion of a localizing entity, and

(II) a nucleic acid sequence of interest; and

(B) introducing said composition into said cell or into a biological system containing said cell.

Claim 291 states the process of claim 290, wherein said potion of the localizing entity (I) is sufficient to permit localization of said nucleic acid product. Claim 292 states the process of claim 290, wherein said nucleic acid product comprises antisense RNA or antisense DNA and said portion of a localizing entity (I) comprises a nuclear localization signalling sequence. Claim 293 states the process of claim 290, wherein said nucleic acid product comprises sense RNA or sense DNA and said portion of a localizing entity (I) comprises a nuclear localization signalling

sequence. Claim 294 states wherein said nucleic acid product comprises sense RNA or sense DNA and said portion of a localizing entity (I) comprises a nuclear localization signalling sequence. Claim 295 states the process of claim 290, wherein said nucleic acid product comprises snRNA. Claim 296 states the process of claim 295, wherein said snRNA comprises U1 or U2 or both. Claim 297 states the process of claim 290, wherein said composition is introduced *ex vivo* into said cell or into a biological system containing said cell. Claim 298 states the process of claim 290, wherein said composition is introduced *in vivo* into said cell or into a biological system containing said cell.

The specification teaches several constructs designed for entry into a cell and expression of one or more sequences to perform a biological function such as antisense inhibition of a nucleic acid. Specifically, several CHENAC constructs are taught prophetically, and pictured in figures 1-13 as vector based constructs constructed by using modified nucleic acid regions and designed to provide improved entry into a cell by way of improved construct-cell interaction. A second group of nucleic acid fused with antibody based constructs are taught prophetically and shown in figures 14-21. Preparation of multimeric insulin by means of nucleic acid hybridization is further taught prophetically and shown in figures 22-23. No exemplification for such constructs is taught in the specification as filed.

Furthermore, vectors ultimately designed for antisense inhibition of HIV in cells by co-expression of antisense DNA under control of a T7 promoter with a T7 polymerase (represented in figures 24-49) are taught and supported by *in vitro* data. Specifically, construction of the M13

phage vectors pRT-A, pRT-B, and pRT-c are taught which contain the coding sequence for the T7 RNA polymerase driven by the RSV promoter and with an SV40 intron sequence that will be spliced out to form a functional polymerase enzyme and each respective construct also having the antisense A, B, and C sequences driven by a T7 promoter and terminated by a T7 terminator. A modified version of the pINT-3 construct (the parent vector of pRT-A, B and C vectors before insertion of the antisense sequences) is taught where a polylinker is inserted behind the poly-A tail of the T7 polymerase gene for subsequent sub-cloning of the lacZ gene in this instance to form pINT-LacZ. The result upon introduction in a eukaryotic cell would be synthesis of the T7 polymerase from the RSV promoter which in turn acts upon the T7 promoter to synthesize B-galactosidase.

Furthermore, plasmids are taught containing anti-sense segments introduced into the transcript region of the U1 gene, plasmid pHSD-4 U1 so that upon expression of the transcript, the antisense RNA sequence is produced to the complementary region of the HIV genome. Specifically, pDU1-A, B, C and D were made using the antisense A, B, and C sequences previously described and D as a control containing a non-HIV sequence. A multi-cassette version of the constructs was also made by sub-cloning in tandem the A,B, and C antisense to make pNDU1 (A,B,C) (N meaning the construct was also contained the gene for neomycin resistance).

Other multi-cassette constructs taught were:

(1) TRI 101, an M13 phage vector containing the "A" antisense T7 operon , the "B" antisense T7 operon and the "C" antisense T7 operon in a single construct (figure 46). Co-

transfection would be required for expression of the antisense molecules from this construct with a vector that expresses T7 RNA polymerase (suggested is the intron containing construct of example 19); and,

(2) an M13 construct constructed from a multi-ligation of portions of pINT-3 (containing the intron containing polymerase) and the T7 promoter driven A, B, and C sequences (see figure 47).

The specification teaches application of some of these constructs ("various U1 constructs described above" p. 167, last line) in antisense inhibition of HIV in infected U937 cell culture. Specifically the following is shown: (1) expression of A, B, and C antisense by hybridization analysis after expression of the "U1 clone" (p. 169, line 3), (2) expression of the "triple U1 construct" (p. 169, para. (c), line 1) which result in a decrease in p24 production next to the control, and increased % reduction in p24 over time and after re-infection of cells, and these results were confirmed by absence p24 amplification next to control cells via PCR of the targeted DNA, and (3) expression of the construct of figure 50, a fusion product antisense A upstream of B-gal gene where antisense activity of the A portion caused inhibition of B-gal activity as shown in lacZ assays. The results in figure 51 show HIV A/Anti-A activity and HIV A/Anti-ABC (when the triple U1 construct was used by *co-transfection*) as the equivalent of the uninfected cells whereas the infected and control containing cells showed high B-gal expression. Therefore, it does not appear in the specification as filed that the multicassette A,B,C and T7 polymerase construct (expressed on same plasmid) was applied to the same HIV challenge experiments.

Additional constructs are more prophetically taught: the primary nucleic acid construct that propagates production centers for the production of single-stranded antisense, etc. in examples 21-25, and the retrovirus vector containing sequences for the expression of antisense RNA directed at HIV on page 181, last para.

Since the only constructs reduced to practice in the specification as filed are the U1-vector-antisense constructs, the instant rejection will focus on the use of these constructs in cells in a whole organism versus cells in cell culture.

There is a high level of unpredictability known in the antisense and relative ribozyme art for *in vivo* (whole organism) applications. The following references primarily refer to the unpredictability of administration of antisense oligonucleotides, but may also be applied to antisense expressed from a vector since the function of the antisense is the same, to locate and bind a target gene, thereby decreasing its expression. The factors considered barriers to successful delivery of antisense delivery to the organism are: (1) penetration of the plasma membrane of the target cells to reach the target site in the cytoplasm or nucleus, (2) withstanding enzymatic degradation, and (3) the ability to find and bind the target site and simultaneously avoid non-specific binding (see Branch). Note also Ma et al. who teach (on page 167) that "to gain therapeutic advantage using antisense-based technology, ODNs must have certain characteristics. They must be resistant to degradation, internalize efficiently, hybridize in a sequence specific manner with the target nucleic acid, display adequate bioavailability with a favorable pharmacokinetic profile and be nontoxic." When expressed from a vector, the

antisense must retain the ability to be localized to the target area. Thus use of U1 introns in the examples in the specification as filed are helpful for targeting the antisense expressed to the nucleus of the cell, but the unpredictability remains for factors such as expression levels of the antisense, the localization of the vector to desired tissues, and expression of the antisense for the recited function, inhibition of the target gene. Flanagan teaches, "oligonucleotides (*in vivo*) are not distributed and internalized equally among organs and tissues.... Unfortunantly, therapeutically important sites such as solid tumors contain very little oligonucleotide following intravenous injections in animals (page 51, column 2)." Ma et al. supports the difficulties of *in vivo* use of ODNs on pages 160-172. Jen et al. further taught that "given the state of the art, it is perhaps not surprising that effective and efficient clinical translation of the antisense strategy has proven elusive. While a number of phase I/II trials employing ONs have been reported..., virtually all have been characterized by a lack of toxicity but only modest clinical effects." (Page 315, col. 2) Green et al. summarizes that "the future of nucleic acid therapeutics using antisense ODNs ultimately depends on overcoming the problems of potency, stability, and toxicity; the complexity of these tasks should now be apparent. Improvements in delivery systems and chemical modifications may lead to safer and more efficacious antisense compounds with improved pharmacokinetics and reduced toxicities." (P. 103, col. B) Note also some of the major outstanding questions that remain in the art taught by Agrawal et al. On page 79, col. 2.

In vitro, antisense specificity to its target may be manipulated by "raising the temperature or changing the ionic strength, manipulations that are commonly used to reduce background

binding in nucleic acid hybridization experiments." (Branch, p. 48) Note also Ma et al. who teach that "*in vitro* subcellular distribution is dependent on the type of ODN modification, cellular system and experimental conditions. ODNs, once internalized, are distributed to a variety of subcellular compartments." (Page 168) Discovery of antisense molecules with "enhanced specificity" *in vivo* requires further experimentation for which no guidance is taught in the specification. Note Branch who teaches the state of the art for designing an antisense which inhibits a target *in vivo:* it "is very difficult to predict what portions of an RNA molecule will be accessible *in vivo*, effective antisense molecules must be found empirically by screening a large number of candidates for their ability to act inside cells (Branch, p.49)." Note Jen et al. who teach that "although mRNA targeting is impeccable in theory, many additional considerations must be taken into account in applying these strategies in living cells including mRNA site selection, drug delivery and intracellular localization of the antisense agent." (Abstract) Bennett et al. further taught that "although the antisense paradigm holds great promise, the field is still in its early stages, and there are a number of key questions that need to be answered and technical hurdles that must be overcome....The key issues concerning this class of chemicals center on whether these compounds have acceptable properties as drugs. These include pharmacokinetic, pharmacological and toxicological properties." (Page 13) As argued above, these issues remain unpredictable in the art for antisense oligonucleotide administration *in vivo*.

One of skill in the art would not accept on its face the successful delivery of the disclosed antisense molecule constructs *in vivo* and further, treatment effects, in view of the lack of

guidance in the specification and the unpredictability in the art. Neither the specification nor technology today teach general guidelines for successful delivery or treatment effects of antisense molecules in whole organisms. Specifically the specification does not teach (1) stability of the antisense molecule constructs *in vivo*, (2)effective delivery to the whole organism and specificity to the target tissues, (3) dosage and toxicity, nor (4) entry of molecule into cell and effective action therein marked by visualization of the desired treatment effects. These key factors are those found to be highly unpredictable in the art as discussed *supra*. The lack of guidance in the specification as filed for these factors would therefore require "trial and error" experimentation beyond which is taught by the specification as filed. Therefore, it would require undue experimentation to practice the invention as claimed.

Response to Arguments

9. Applicant's arguments filed June 18, 2002, have been fully considered but they are not persuasive.

Applicant's state that "it would not require undue experimentation for the ordinary skilled artisan to practice the invention. A sufficiently detailed description is provided in the specification for preparing and using the constructs of the present invention, including their entry into eukaryotic cells for expression of sequence for biological function. The description and use of the claimed constructs runs to examples and even figures. Applicants attach hereto a decision tree provided with "Training Materials for Examining Patent Applications with respect to 35

U.S.C. Section 112, First Paragraph-Enablement Chemical/Biotechnical Applications". Two questions are posed on the decision tree. The first is "Does the specification teach how to make and use at least one embodiment encompassed by the claims as a whole without undue experimentation?" Clearly, the specification has taught one of ordinary skill in the art how to make and use more than one embodiment. The second question is "Are the enabled embodiments representative of the full scope of the claims?" Again the answer is yes. The methods described for obtaining the disclosed constructs could be applied to obtaining any of the constructs encompassed by the pending claims. Therefore, the scope of the present composition claims is deemed appropriate."

In response, the MPEP 2164.01(a) teaches the determination of whether or not one of skill in the art would necessarily practice undue experimentation to make and use the breath of the claimed compounds. As reiterated above in more detail, there is a high level of unpredictability in the art of antisense/ribozyme construction for use in a whole organism, and thus for use in a cell in a whole organism. Since the examples primarily refer to antisense in the specification as filed, the above rejection focuses on the expression of antisense or ribozymes from the claimed constructs.

In regards to the Branch and Flanagan references previously cited and reiterated above, applicant argues that they "were actually published after the priority date of the above-referenced application. The MPEP 2164.05(a) states that "the state of the prior art existing at the filing date of the application is used to determine whether a particular disclosure is enabling as of the filing

date." This section further states "In general, the examiner should not use post-filing date reference to demonstrate that the patent is no-enabling.""

In response, the Branch, Flanagan and other newly cited references above are relied upon to teach that even today, there is a high level of unpredictability in the art for design and use of antisense in whole organisms due to the complexity of the whole organism environment and the number of unpredictable factors argued above.

Applicants further "assert that there are a number of publications available as of the priority date of the above-referenced application which express a more optimistic attitude regarding the suitability of antisense to become useful in therapeutic application. One example of such a publication is Crooke, 1994, Antisense Research and Development 4:145-6, attached hereto as Exhibit 1. Another example is Liu et al., 1997, J. Virol. 71:4079-4085, attached hereto as Exhibit 2 which discloses Tat-activated expression of chloramphenicol acetyltransferase was shown to be specifically inhibited in cells expressing Tat and transactivation response region antisense sequences."

In response, the Liu et al. article is a publication of the constructs and experiments taught in the instant specification. However, the Liu et al. paper does not further provide any *in vivo* context of use for the disclosed constructs. While they state on page 4085 that "[t]he choice of U1 as an antisense carrier provided structural stability and nuclear localization", they further state that "[t]his successful approach in cell culture is being developed as means of achieving a high level of stable resistance in patent cells for the purpose of developing an ex vivo therapy for

treating HIV infections." Thus, the *in vivo* uses are "being developed" and were not show at the time the invention was made to function *in vivo*. The Crook reference does not further provide an specific expectation of success for the instantly disclosed constructs to function *in vivo* either.

Applicant further states that "It is also Applicants' position that *in vivo* data is not necessary. As noted in the MPEP Section 2107.03, III, "Office personnel should be careful not to find evidence unpersuasive simply because no animal model for the human disease condition had been established prior to the filing of the application." However, Applicants do note that clinical trials were being conducted by the assignee of the instant application around its priority date (Exhibit 4). The results have been favorable and a number of public announcements have been made concerning the ongoing clinical trials and results."

The above rejection does not imply that an animal model of a disease is needed to enable the instantly claimed invention. The rejection is centered on the ability to a make and use the claimed methods with any expression construct as claimed, and the position has been maintained, based on the references cited, that there is a high level of unpredictability in the art of design and use of antisense in a whole organism. Although applicants state that clinical trials are underway, the information in Exhibit 4 does not teach what constructs are in trials and whether or not they function as instantly claimed in the context of a whole organism.

Claim Rejections - 35 USC § 102

A person shall be entitled to a patent unless -

(e) the invention was described in (1) an application for patent, published under section 122(b), by another filed in the United States before the invention by the applicant for patent or (2) a patent granted on an application for patent by another filed in the United States before the invention by the applicant for patent, except that an international application filed under the treaty defined in section 351(a) shall have the effects for purposes of this subsection of an application filed in the United States only if the international application designated the United States and was published under Article 21(2) of such treaty in the English language.

10. Claims 265-270, 272-276, 278-280, 282-284 and 288-295 are rejected under 35 U.S.C. 102(e) as being anticipated by Sullenger et al. (U.S. Patent 5,854,038).

Claim 265 is drawn to a composition of matter comprising a nucleic acid component which when present in a cell produces a non-natural nucleic acid product, which product comprises (I) a cellular compartment localizing entity, and (ii) a nucleic acid sequence of interest. Claim 266 states that the cellular compartment localizing entity (I) is sufficient to permit localization of said non-natural nucleic acid product. Claim 268 states that the nucleic acid of interest (ii) is selected from the group consisting of DNA, RNA, a DNA-RNA hybrid, a DNA-RNA chimera, and combination of the foregoing. Claim 272 states that the non-natural nucleic acid product is single-stranded. Claim 273 states that the non-natural nucleic acid product is selected from the group consisting of antisense RNA, antisense DNA, sense RNA, sense DNA, a ribozyme, a protein binding nucleic acid sequence, and a combination of the foregoing. Claim 278 states the nucleic acid component of claim 265 is selected from a nucleic acid, a nucleic acid construct, a nucleic acid conjugate, a virus, a viral fragment, a viral vector, a viroid, a phage, a

phage, a plasmid, a plasmid vector, and a bacterial fragment, or a combination of the foregoing. Claim 279 states wherein said nucleic acid is selected from the group consisting of DNA, RNA, a DNA-RNA hybrid, a DNA-RNA chimera, and a combination of the foregoing. Claim 290 is drawn to a process for localizing a nucleic acid product in a eukaryotic cell, comprising:

(A) providing a composition of matter comprising a nucleic acid component which when present in a cell produces a non-natural nucleic acid product, which product comprises:

(I) a portion of a localizing entity, and

(II) a nucleic acid sequence of interest; and

(B) introducing said composition into said cell or into a biological system containing said cell. Claim 291 states the process of claim 290, wherein said potion of the localizing entity (I) is sufficient to permit localization of said nucleic acid product.

Sullenger et al. taught in column 3, lines 8-37, specifically lines 15-20, that "[t]hese localication signals may be tethered to the therapeutic agent by any desired procedure, for example, by construction of a DNA template which produces both the localization signal and therapeutic agent RNA as part of the same RNA molecule. They taught in col. 2, lines 38-48, that the therapeutic agents that are localized in an appropriate compartment with a vial target include RNA molecules such as decoy RNAs, ribozymes and antisense RNA or DNA molecules.

Claim 267 states the localizing entity (I) comprises a nuclear localization signalling sequence. Claim 9 of '038 states "[a] therapeutic agent comprising a localization signal, wherein said localization signal is capable of localizing said therapeutic agent in the same cellula

compartment as the target molecule of said therapeutic agent in a cell in vitro. Thus, since a nucleic acid is produced in the nucleus, claim 9 inherently embraces instant claim 267 for producing a nucleic acid theapeutic such as an antisense or ribozyme that binds the target nucleic acid expressed in the nucleus compartment of the cell. Claim 269 states that RNA comprises a nuclear localized RNA complexed with protein molecules. Claim 270 states that the nuclear localized RNA comprises a snRNA. Claim 275 states that the non-natural nucleic acid product comprises antisense RNA or antisense DNA and the localizing entity (I) comprises a nuclear localization signalling sequence. Claim 292 states the process of claim 290, wherein said nucleic acid product comprises antisense RNA or antisense DNA and said portion of a localizing entity (I) comprises a nuclear localization signalling sequence. Claim 293 states the process of claim 290, wherein said nucleic acid product comprises sense RNA or sense DNA and said portion of a localizing entity (I) comprises a nuclear localization signalling sequence. Claim 294 states wherein said nucleic acid product comprises sense RNA or sense DNA and said portion of a localizing entity (I) comprises a nuclear localization signalling sequence. Claim 295 states the process of claim 290, wherein said nucleic acid product comprises snRNA. In col. 10 of Sullenger et al., lines 57-58, they further teach use of "localization to nuclear compartment utilizing antigen binding site found on most snRNAs". See also col. 3, lines 5-7, which teach localization to "a nucleus at the location of synthesis of the target."

Claim 274 states that protein binding nucleic acid sequence comprises a decoy that binds a protein required for a viral assembly or viral replication. In col. 2, line 44, use of a decoy was

taught by Sullenger et al. They disclose throughout the specification where the therapeutic agent is used for inhibition of a viral agent, and specifically in col. 2, lines 21-24, where the "RNA-based inhibitors of viral replication can be localized by use of a viral packaging signal, or other equivalent element, to place the inhibitory RNA in the same location as the target RNA."

Claim 276 states the non-natural nucleic acid product comprises antisense RNA or antisense DNA and the localizing entity (I) comprises a cytoplasmic localization signalling sequence. In col. 10, line 49, Sullenger et al. also teaches localization to either the nucleus or the cytoplasm of the cell.

Claim 280 states the composition of claim 278, wherein the nucleic acid is modified. In col. 11, lines 7-38, Sullenger et al. teaches use of chemical modifications of the nucleic acids used.

Claim 282 states the composition of claim 265, wherein the production of said nucleic acid product is mediated by a vector. Claim 283 states the composition of claim 282, wherein the vector is selected from the group consisting of a viral vector, a phage vector, a plasmid vector and a combination thereof. In col. 6, lines 7-31, Sullenger et al. taught that plasmid vectors may be used to expressed the localized nucleic acid constructs.

Claim 284 is drawn to a cell containing the composition of claim 265. Claim 288 is drawn to a biological system containing the cell of claim 284. Claim 289 states that the system is selected from the group consisting of an organism, an organ, a tissue, a culture, and a combination thereof. Sullenger et al. taught throughout the specification that their constructs are

for use in targeting cells, and specifically, locations within cells, or specific tissues, with their disclosed therapeutic nucleic acid targeted constructs.

11. Claims 245-249, 251-256, 258-261, 264-273, 275, 278-279, 282-283, 284, 288, 289, 290-296, 299, 300, 302, 303, 308, 312 and 313 are rejected under 35 U.S.C. 102(b) as being anticipated by DeYoung et al. (*Biochemistry* Vol. 33, pp. 12127-12138, 1994).

Claims 245 and 246 are drawn to a composition comprising a primary nucleic acid component which upon introduction into a eukaryotic cell produces a secondary nucleic acid component which is capable of producing a nucleic acid product, or a tertiary nucleic acid component, or both, in said eukaryotic cell, wherein said primary nucleic acid component is not obtained with said secondary or tertiary compoent or said nucleic acid product. Since the composition comprising the primary nucleic acid component which upon introduction into a eukaryotic cell produces a secondary nucleic acid component which is merely 'capable of' producing a nucleic acid product, or a tertiary nucleic acid component or both, the language 'capable of' implies a latent characteristic of the claimed nucleic acid composition, but does not require this property.

De Young et al. taught on page 12128, col. 1, that "[w]e report here the use of U1 and T7 vector systems to direct the expression of ribozyme constructs of limited and defined size that are sufficiently stable to efficiently cleave ANF mRNA in cells. These vector systems ... should be applicable to the selective suppression of other desired genes, either for physiological studies or

for therapeutic purposes." In figure 3, page 12129, they taught the vector constructs used for expression of the U1-ribozyme constructs. Thus they taught the instantly claimed primary and secondary nucleic acid component claimed (the primary is the vector, the secondary is the expressed U1-ribozyme in the cell).

Claim 247 specifies that the primary composition is a nucleic acid , a nucleic acid construct, a plasmid, a plasmid vector, etc. De Young et al. teaches use of plasmid vectors (figure 3, page 12129).

Claim 248 states wherein the primary nucleic acid component is single-stranded, double-stranded or partially double stranded. The plasmids of De Young et al. are double stranded.

Claim 249 states that the primary nucleic acid component is DNA, RNA, nucleic acid analogs or a combination thereof. The plasmids of De Young et al. are DNA.

Claim 251 states the the secondary nucleic acid component is DNA, RNA, a DNA-RNA hybrid, a DNA-RNA chimera or a combination of the forgoing. The U1-ribozyme products expressed by the plasmids of De Young et al. are RNA secondary products.

Claim 252 states that the composition further comprises a signal processing sequence. DeYoung et al. explain on page 12136, col. 1, that the "[i]n this study we have evaluated the use of U1 and T7 vector systems for expressing ribozymes.... The U1 vector system used in this study has advantages for directing the expression of short, defined transcripts in high copy number. The U1 gene is a member of a class of small nuclear RNAs (UsnRNAs) that are ubiquitously expressed under the control of a strong RNA polymerase II promoter and play and

important role in the processing of precursor RNAs." Since the instant specification teaches use of the same U1 constructs and refers to them as signal processing sequences, it would have been inherent to one skilled in the art that the U1 sequences used by DeYoung et al. were also considered signal processing sequences. Furthermore, claim 253 specifies that the signal processing sequence is an intron, and the U1 sequence taught by DeYoung et al. is an intron sequence. De Young et al. further anticipates claim 254 since they taught that the U1 signal processing sequence is in the secondary nucleic acid component. They further anticipate claim 255 since they taught that the ribozyme sequence product is produced, which is single-stranded. They further anticipated claim 256 since they teach production of a ribozyme. They further anticipated claims 258 and 259 since they taught use of a plasmid vector to express the U1-ribozyme constructs.

De Young et al. further anticipated claim 260 since they taught expression of their U1-ribozyme constructs in COS-1 cells (page 21130, col. 2). They further anticipated claim 264 since they taught the ribozyme sequences expressed from their vectors.

De Young et al. further anticipated claims 265-267 and 269-271 since they taught a composition of matter comprising a nucleic acid component (the vectors in figure 3) which when present in a cell produces a non-natural product (the U1-ribozyme constructs), which product comprises (I) a cellular compartment localizing entity (the U1 snRNA sequence which localizes to the nucleus), and (ii) a nucleic acid sequence of interest (the ribozyme sequence). The further taught claim 268 since the nucleic acid ribozyme expressed is an RNA sequence. They further

anticipated claims 272-273 since the ribozyme produced was a single-stranded ribozyme. They are further considered to anticipate instant claim 275 since they taught expression of a ribozyme, which is a kind of antisense RNA, since it functions as an antisense, complementary, strand to the expressed sequence. They further anticipate instant claim 278 since they taught wherein the nucleic acid component is a nucleic acid , a nucleic acid construct and a plasmid/plasmid vector. They further anticipate instant claim 279 since they taught that the nucleic acid is a DNA (and the expressed nucleic acid is an RNA). They further anticipate instant claim 282 since they taught that the production of the nucleic acid product is mediated by a vector. They further anticipate claim 283 since they taught that the vector is a plasmid vector. They further anticipate claims 284, 288 and 289 since they taught expression of the vectors in COS cells, a culture of said cells.

De Young et al. further anticipated claims 290-296 since the process of expressing their plasmid U1snRNA-ribozyme constructs in the COS cells meets all the limitations of these claims as discussed above, and U1constructs localize to the nucleus.

Claim 299 is anticipated by De Young et al. since their plasmid U1snRNA constructs are nucleic acid components which upon introduction into a cell express the ribozyme constructs. Since the language used in claim 299, 'capable of', is a latent characteristic as claimed, the claim broadly embraces any nucleic acid component such as those taught by De Young et al. Furthermore, De Young et al. anticipates instant claim 300 since the single-stranded nucleic acids of interest are the ribozymes taught by De Young et al. They further anticipate claim 302 and 303 since they taught the vectors which were made of DNA nucleic acids. They further

anticipated claim 308 since they taught that the ribozymes were the nucleic acid sequence product expressed and ribozymes are capable of acting as antisense. They further anticipated claim 312 since they taught that the products expressed were ribozymes. They further anticipated claim 313 since they taught delivery of the vector constructs to COS-1 cells in cell culture.

12. Claims 245, 249, 250, 265, 276, 277, 279, 280 and 314-316 are rejected under 35 U.S.C. 102(e) as being anticipated by Hinuma et al. (U.S. Patent 6,538,107).

Claim 245 is drawn to a composition comprising a primary nucleic acid component which upon introduction into a eukaryotic cell produces a secondary nucleic acid component which is capable of producing a nucleic acid product, or a tertiary nucleic acid component, or both, in said eukaryotic cell, wherein said primary nucleic acid component is not obtained with said secondary or tertiary component or said nucleic acid product. Claim 249 states the compositon of claim 245, wherein said primary nucleic acid component is selected from the group consisting of DNA, RNA, nucleic acid analogs, and a combinantion thereof. Claim 250 states the composition of claim 249, wherein said DNA, RNA or both are modified.

Claim 265 is drawn to a composition of matter comprising a nucleic acid component which when present in a cell produces a non-natural nucleic acid product, which product comprises (I) a cellular compartment localizing entity, and (ii) a nucleic acid sequence of interest. Claim 276 is drawn to the composition of claim 273, wherein said non-natural nucleic acid product comprises antisense RNA or antisense DNA and said localizing entity (I) comprises a

cytoplasmic localization signalling sequence. Claim 277 is drawn to the composition of claim 273, wherein said non-natural nucleic acid product comprises sense RNA or sense DNA and said localizing entity (I) comprises a cytoplasmic localization signalling sequence. Claim 279 states the composition of claim 265, wherein said nucleic acid component is selected from a nucleic acid, a nucleic acid construct, a nucleic acid conjugate, a virus, a viral fragment, a viral vector, a viroid, a phage, a phage, a plasmid, a plasmid vector, and a bacterial fragment, or a combination of the foregoing. Claim 280 is drawn to the composition of claim 278 wherein said nucleic acid is modified.

Claim 314 is drawn to a construct which when present in a cell produces a product, said construct being bound non-ionically to an entity comprising a chemical modification or a ligand. Claim 315 is drawn to the construct of claim 314, having at least one terminus, said terminus comprising a polynucleotide tail. Claim 316 is drawn to the construct of claim 315, wherein said polynucleotide tail is hybridized to a complementary polynucleotide sequence.

Hinuma et al. teaches in col. 105-106 that antisense oligonucleotides (nucleic acids) capable of inhibiting the replication or expression of G protein coupled receptor protein gene. They state that the "relationship between the target and oligonucleotides complementary to at least a portion of the target, specifically hybridizable with the target, is denoted as "antisense"." (col. 105, lines 31-34) They state that the antisense "may include double- and single-stranded DNA, as well as double- and single-stranded RNA and DNA:RNA hybrids, and also include, as well as unmodifed forms of the polynucleotide or oligonucleotide, known types of madifications,

for example, labels which are known to those skilled in the art, "caps", methylation, substitution of one or more of the naturally occurring nucleotides with analogue, internucleotide modifications such as, for example, those with uncharged linkages (e.g., methyl phosphonates, phosphotriesters, phosphoramidates, cabamates, etc.) and with charged linkages or sulfur-containing linkages (e.g. phosphorrothioates, phophorodithioates, etc.), those containing pendant moietes, such as, for example, proteins (including nucleases, nuclease inhibitors, toxins, antibodies, signal peptides, poly-L-lysine, etc.) and saccharides (e.g. monosaccharides, etc._), those with intercalators (e.g., acridine, psoralen, etc.), those containing chelators (e.g., metals, radioactive metals, boron, oxidative metals, etc.), those containing alkylators, those with modified linkages (e.g., alpha anomeric nucleic acids, etc.)." (Col. 105, lines 44-64) See also the rest of col. 105 and col. 106 for additional information taught by Hinuma et al. for the modification of such antisense.

Thus, Hinuma et al. taught all the elements of the instantly claimed invention since they taught double-stranded (complementary, hybridized) oligonucleotides which are tails since they are linear and have an end. These oligonucleotides may be modified with covalently bound moieties such as antibodies or signal peptides and also when in a cell are capable of producing a product by the antisense action of the molecules which decreases expression of the target gene (thus the product is the decreased gene expression) and/or other actions of the attached molecules. Since they taught conjugation with signal peptides, they taught use of these conjugates for direction to a particular cellular compartment.

Claim Rejections - 35 USC § 103

13. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

14. Claims 245, 256, 257, 265, 317, 273 and 274 are rejected under 35 U.S.C. 103(a) as being unpatentable over Sullenger et al. (U.S. Patent 5,854,038) or DeYoung et al. (*Biochemistry* Vol. 33, pp. 12127-12138, 1994) in view of ter Meulen et al. (U.S. Patent 5,646,032).

Claim 245 is drawn to a composition comprising a primary nucleic acid component which upon introduction into a eukaryotic cell produces a secondary nucleic acid component which is capable of producing a nucleic acid product, or a tertiary nucleic acid component, or both in said eukaryotic cell, wherein said primary nucleic acid component is not obtained with said secondary or tertiary component or said nucleic acid product. Claim 256 states the composition of claim 245, wherein said nucleic acid product is selected from the group consisting of antisense RNA, antisense DNA, a ribozyme, a protein binding nucleic acid sequence, and a combination of the foregoing. Claim 257 states the composition of claim 256, wherein said protein binding nucleic acid sequence comprises a decoy that binds a protein

required for viral assembly or viral replication. Claim 317 states the composition of claim 245, wherein said secondary nucleic acid is DNA and said tertiary nucleic acid is RNA.

Claim 265 is drawn to a composition of matter comprising a nucleic acid component which when present in a cell produces a non-natural nucleic acid product, which product comprises (I) a cellular compartment localizing entity, and (ii) a nucleic acid sequence or interest. Claim 273 states the composition of claim 265, wherein said non-natural nucleic acid product is selected from the group consisting of antisense RNA, antisense DNA, sense RNA, sense DNA, a ribozyme, a protein binding nucleic acid sequence, and a combination of the foregoing. Claim 274 states the composition of claim 273, wherein said protein binding nucleic acid sequence comprises a decoy that binds a protein required for a viral assembly or viral replication.

Sullenger et al. taught in column 3, lines 8-37, specifically lines 15-20, that "[t]hese localization signals may be tethered to the therapeutic agent by any desired procedure, for example, by construction of a DNA template which produces both the localization signal and therapeutic agent RNA as part of the same RNA molecule. They taught in col. 2, lines 38-48, that the therapeutic agents that are localized in an appropriate compartment with a viral target include RNA molecules such as decoy RNAs, ribozymes and antisense RNA or DNA molecules.

They did not teach that the target was a viral replication gene/agent.

ter Muelen et al. taught in col. 4, lines 17-25, that "decoy RNA may be used that contains particular nucleotide base sequences which, for their part, bind virus proteins which are essential for the replication of a pathogenic virus. Thus, decoy RNA sequences can, for example, contain

multiple copies of the TAR nucleotide base sequence and the REV responsive element nucleotide base sequence (RRE) from HIV and competitively bind the tat and rev regulatory proteins of HIV, and thereby lower the rate of replication of HIV in the infected cell."

It would have been *prima facie* obvious to one of ordinary skill in the art to substitute the antisense or decoy RNA and/or DNA molecule taught by Sullenger et al. with the decoy taught by ter Muelen et al. directed against a viral replication target since Sullenger taught the design of decoys generally to any viral target, and as ter Muelen et al. taught, the viral replication protein is an essential molecule for the replication of the virus and targeting this sequence with a decoy allows for competitive binding to lower the rate of viral replication in the infected cell.

One of ordinary skill in the art would have been motivated to inhibit an infectious virus as taught both by Sullenger et al. and ter Muelen et al. with agents such as decoys to inhibit the virus. Although Sullenger et al. does not explicitly recite targeting viral replication *per se*, ter Muelen et al. taught that one of ordinary skill in the art would have been motivated to target viral replication using decoys for the benefits of lowering the rate of replication of the virus in the infected cell.

One of ordinary skill in the art would have had an expectation of success to use the decoy constructs taught by Sullenger et al. to produce a decoy in a virally infected cell such as taught by ter Muelen et al. for the purpose of lowering the rate of the replication of the virus in the infected cell.

15. Claims 262, 263, 286, 287, 297 and 298 are considered free of the prior art since the prior art did not teach nor fairly suggest the *ex vivo* and *in vivo* administration of the claimed compounds. Claims 301 and 304-307 and 309-311 are considered free of the prior art since the closest prior art, De Young et al. cited above for claims 299, 303 and 308, does not teach nor fairly suggest the additional claimed limitations.

16. Any inquiry concerning this communication or earlier communications from the examiner should be directed to *Mary M. Schmidt*, whose telephone number is (703) 308-4471.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, *John LeGuyader,* may be reached at (703) 308-0447.

Any inquiry of a general nature or relating to the status of this application should be directed to *Katrina Turner*, whose telephone number is (703) 305-3413.

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M. M. Schmidt
April 30, 2003